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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,970	YIP ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,12,20 and 84-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,12,20 and 84-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 6/26/2006 in response to the previous Non-Final Office Action (3/24/2006) is acknowledged and has been entered.

Claims 1, 8, 12, 20 and 84-94 are currently pending and under consideration.

The Declaration Under CFR 1.132 filed on 06/26/2006 by the inventor, Dr. Tai-Tung Yip is acknowledged and has been considered. The Declaration by Dr. Tai-Tung Yip sets forth the primary concerns addressed by the Examiner in the rejection of claims 1, 8, 12, 20 and 84-94 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement in the previous Non-Final Office action. Specifically, the Declaration addressed the following issues: 1) Is the phenomenon of an abundance of lower weight proteins in prostate cancer samples detectable with other MS probe surfaces; 2) Is the phenomenon of an abundance of lower weight proteins in prostate cancer samples detectable in other patients; 3) Is the phenomena of an abundance of lower weight proteins in prostate cancer patients detectable in samples other than serum; and 4) Secondary issues.

With regards to the declaration, the Examiner greatly appreciates Dr. Tai-Tung Yip's declaration. However, the Declaration by Dr. Tai-Tung Yip has not been found fully persuasive to over come the enablement rejection and will be fully addressed below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is

either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 8, 12, 20 and 84-94 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1-14 of copending Application No. 10/221,905.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. For example, the specific protein markers having a molecular weight of 97402.68, 9752.30, 8766.93, 6277.97, or 2781.72 Da claimed in the conflicting application anticipates the genus of a markers having an apparent molecular weight of less than 10,000 Da claimed in the application being examined.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response to this rejection, Applicants assert that they believe that the subject application will be the first to issue and reserve the right to file a terminal disclaimer at the appropriate time during prosecution of the 905 application.

Thus, the rejection of Claims 1, 8, 12, 20 and 84-94 as being provisionally rejected on the ground of nonstatutory obviousness-type double patenting is maintained.

Claims 1, 8, 12, 20 and 84-94 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1-8 of copending Application No. 10/505,367.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. For example, the specific protein markers having a

molecular weight of 3448, 4036, ... 8445 Da claimed in the conflicting application anticipates the genus of a markers having an apparent molecular weight of less than 10,000 Da claimed in the application being examined.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 8, 12, 20 and 84-94 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1-8 of copending Application No. 10/513,649.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. For example, the specific protein markers having a molecular weight of 4475, 5074, 5382, ... 9656 Da claimed in the conflicting application anticipates the genus of a markers having an apparent molecular weight of less than 10,000 Da claimed in the application being examined.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Rejections Upon Reconsideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, 12, 20 and 84-94 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps in claim 1 is: a correlation step describing how the results of the method relate back to the preamble of the method objectives. For example, it is unclear how determining whether the test amount is a diagnostic amount is consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8, 12, 20 and 84-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of markers, i.e., polypeptides, obtained from a sample selected from prostate tissue, blood, serum, semen, seminal fluid or seminal plasma characterized by an apparent molecular weight of less than 10,000 Da which can be used as a diagnostic marker to discriminate between prostate cancer and benign prostate hyperplasia. However, the written description in this case only sets forth a representative number of species of peptide obtained from seminal plasma characterized by a molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da.

The specification teaches (page 2, line 33 to page 3, line 1) that specific markers of the invention include, but are not limited to, peptides which are present at elevated levels in samples from prostate cancer patients compared to samples from BPH patients. The specification further discloses (page 2, lines 30-33 and page 3, lines 10-11) that suitable markers include not only polypeptides having an apparent molecular weight of less than 27,000 Da, but also polypeptides which are generated by PSA-mediated proteolysis such as the cleaved product generated by PSA-mediated proteolysis of semenogelin I. Specifically, the specification teaches peptide markers obtained from seminal plasma from a prostate cancer patient and not present in seminal plasma of a benign prostate hyperplasia patient having a molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da (Examples A-C). Thus, while the written description (beginning on page 30, Examples) in this case clearly sets forth peptides obtained from a seminal plasma sample having a molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da which can be used for the diagnosis of prostate cancer versus benign prostate hyperplasia, the specification does not appear to reasonably convey possession any and/or all protein markers from any sample.

As such, the specification is not commensurate with the full scope as claimed. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of polypeptides that encompass the genus of markers having an apparent molecular weight of less than 10,000 Da which are differentially expressed nor does it provide a description of structural features that are common to the markers. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of markers, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicants should further refer to the revised interim Written Description Guidelines regarding protein variant language (see http://www.uspto.gov/web/menu/written.pdf).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a peptide obtained from seminal plasma characterized by a molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1, 8, 12, 20 and 84-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing prostate cancer versus benign prostate hyperplasia, the method comprising: (i) obtaining from a subject suspected of having either prostate cancer or benign prostate hyperplasia a sample containing a plurality of prostate related protein markers having apparent molecular weights below 10,000 Da, wherein the sample is from seminal plasma; (ii) determining by mass spectroscopy the intensity of the signal for mass/charge ratios of the plurality of protein markers in the sample, the protein having an apparent molecular weight of less than 10,000 Da; (iii) comparing the intensity of the signal for mass/charge ratios of the plurality of protein markers having apparent molecular weight markers of less than 10,000 obtained from step (ii) with the intensity of the signal for mass/charge ratios of the plurality of protein markers having apparent molecular weight markers of less than 10,000 from a control sample where the control sample originates from benign prostate hyperplasia; and (iv) determining whether the comparisons of intensity of the signal for mass/charge ratios obtained in step (iii) is a diagnosis of prostate cancer versus benign prostate hyperplasia, wherein a sample from seminal plasma having a protein characterized by molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da is a diagnostic of prostate cancer, does not reasonably provide enablement for a method of diagnosing prostate cancer versus benign prostate hyperplasia, the method comprising : (i) obtaining from a subject a sample containing a plurality of prostate related protein markers having apparent molecular weights below

10,000 Da, wherein the sample is selected from the group consisting of prostate tissue, blood, serum, semen, seminal fluid or seminal plasma; (ii) determining by mass spectroscopy a test amount of the plurality of protein markers in the sample, the protein having an apparent molecular weight of less than 10,000 Da; (iii) comparing the test amount of the plurality of protein markers having apparent molecular weight markers of less than 10,000 from a control sample where the control sample originates from benign prostate hyperplasia; and (iv) determining whether the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance,

predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of diagnosing prostate cancer versus benign prostate hyperplasia, wherein a sample containing a plurality of proteins having apparent molecular weights below 10,000 Da is compared to a control sample containing a plurality of proteins having apparent molecular weights below 10,000 Da where the control sample originates from benign prostate hyperplasia. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a a method of diagnosing prostate cancer versus benign prostate hyperplasia, the method comprising : (i) obtaining from a subject a sample containing a plurality of prostate related protein markers having apparent molecular weights below 10,000 Da, wherein the sample is selected from the group consisting of prostate tissue, blood, serum, semen, seminal fluid or seminal plasma; (ii) determining by mass spectroscopy a test amount of the plurality of protein markers in the sample, the protein having an apparent molecular weight of less than 10,000 Da; (iii) comparing the test amount of the plurality of protein markers having apparent molecular weight

markers of less than 10,000 from a control sample where the control sample originates from benign prostate hyperplasia; and (iv) determining whether the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia. As such, the "test amount" is used to determining whether one suffers from prostate cancer or benign prostate hyperplasia.

Guidance in the specification and Working Examples

The specification teaches that the invention provides methods for aiding a prostate cancer diagnosis, which comprises determining a test amount of a marker in a sample from a subject and determining whether the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer (page 2, lines 25-29). With regards to the "test amount", the specification teaches a "test amount of a marker refers to an amount of a marker present in a sample being tested, wherein the test amount can be either in absolute amount or relative amount (page 8, lines 27-29). The specification further teaches (beginning on page 30, Examples) that protein markers were identified using a Ni(II) ProteinChip® Array, H4 ProteinChip® array, and a SCX1 ProteinChip® array, wherein the samples, specifically seminal plasma, were obtained from one BPH (benign prostate hyperplasia) patient and one patient with prostate cancer. With regards to the Ni(II) ProteinChip ® array, the specification teaches (page 30, line 28 to page 32, line 12 and Figure 4) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 8030 Da and 8714 Da, were found to be very abundant in the sample from the prostate cancer patient than in the sample from the BPH patient. Moreover, the specification teaches (page 30, line 28 to page 32, line 12 and Figure 4) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 2905 Da, 3038 Da, 3600 Da, 3835 Da, 3933 Da and 4175 Da, were found to be very abundant in the sample from the BPH patient than a sample from the prostate cancer patient. With regards to the H4 ProteinChip ® array, the specification teaches (page 32, line 15 to page 33, line 23, and Figure 5) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da and 8240 Da were found to be very abundant in the sample from the prostate cancer patient than the samples from the BPH patient. Furthermore, the specification teaches (page 32, line 15 to page 33, line 23, and Figure 5) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 6098 Da, 6270 Da, 6998

Da, 7843 Da and 8030 Da were also bound and detected using the Ni (II) ProteinChip ® array. With regards to SCX1 ProteinChip® array, the specification teaches (page 33, line 25 to page 34, line 23 and Figure 6) that a protein having an apparent molecular weight of about 5753 Da was present at a high level (relative intensity of about 52) in the sample of the prostate cancer patient. Thus, while the specification clearly teaches that a sample obtained from seminal plasma having a protein characterized by a molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da is a diagnostic of prostate cancer versus benign prostate hyperplasia, the specification appears to be silent on any other proteomic profiles obtained from any sample which can be used for a diagnostic amount consistent with the diagnosis of prostate cancer versus benign prostate hyperplasia.

Quantity of experimentation

The quantity of experimentation in the area of proteomics for diagnosis and/or differentiation of prostate cancer vs. benign prostate hyperplasia is extremely large given the infancy of using this technology for diagnostic purposes.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize the unpredictability of using proteomic profiling in a diagnostic setting. For example, Diamandis, E.P. (J. National Cancer Institute 2004; 96: 353-356, *of record*) discusses the potential problems in the analysis of serum proteomic patterns for early cancer diagnosis. These problems for identifying tumor markers include the mechanisms by which tumor markers are released into the circulation, their abundance in biologic fluids, their metabolism and excretion, their dynamic relationship within the host, the clinical samples used, the mass spectrometry instrument and/or the bioinformatic analysis (page 353, 1st column, 3rd paragraph). For instance, Diamandis teaches that discrepancies in the discriminatory peaks (i.e., peaks representing molecules that appear or disappear during cancer progression, or whose amounts differ in cancerous versus noncancerous tissue) identified by four different papers by three different research groups suggests that serum proteomic patterns obtained by the SELDI-TOF technique may not be reproducible within a group or among groups of investigators for the same type of cancer, even when the general analytical methods or datasets are

the same (page 353, 1st column, 4th paragraph). Regarding the clinical samples, Diamandis teaches that it is still unknown whether the proteomic patterns will differ between plasma and serum, or how they are affected by the number of freeze thaw cycles or its length of storage (page 354, 1st column, last paragraph). More recently, Diamandis et al. (Clinical Cancer Research 2005; 11: 963-965, *of record*) teach that while the original papers on serum proteomic profiling for diagnosis of various forms of cancer reported impressive results, these results have not been reproduced by other laboratories and the method has not been validated (page 964, 2nd column, 1st full paragraph). Specifically, Diamandis et al. teach that using peaks of unknown identity for diagnostic purposes should not be a reason a reason to invalidate the method; instead, as Ranshoff points out, it will be important to examine "if this technology does work" and leave the question of "how it works" for investigation at a later time. However, Diamandis points out that precautionary measures about sample collection, processing, and patient selection must be seriously considered to avoid biases (page 964, 2nd column, 1st full paragraph). Along the same lines, Grizzle et al. (Cancer Informatics 2005; 1: 86-97, *of record*) teach that the use of any multiplex mass spectroscopy based approach, as in the analysis of bodily fluids to detect a disease, must be analyzed with great care due to the susceptibility of multiplex and mass spectroscopy methods to biases introduced via experimental design, patient samples, and/or methodology (abstract) In particular, Grizzle et al. teach that specific biases include those related to experimental design, patients, samples, protein chips, chip reader and spectral analysis (abstract). Regarding the biases based on patients, Grizzle et al. teach that these biases include demographics (e.g., age, race, ethnicity, sex), homeostasis (e.g., fasting, medications, stress, time of sampling), and the site of analysis (hospital, clinic other) (beginning on page 88, 2nd column to page 92, 1st column). Regarding the biases in samples, Grizzle et al. teach that the biases in samples include conditions of sampling (type of sample container, time of processing, time to storage), conditions of storage (time and temperature of storage), and prior manipulation (freeze thaw cycles)(beginning on page 92, 1st column to page 93, 1st column), experimental design, patient samples, and/or methodology (abstract). These references demonstrate that there are a number of different biases that need to be considered prior to providing a diagnosis of a diseases based on proteomic profiling.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Note: The instant rejection of claims 1, 8, 12, 20 and 84-94 has changed from an enablement rejection to a scope of enablement rejection. However, in order to advance prosecution, the Examiner has included Applicants arguments, as well as, a response to these arguments.

In response to the previous rejection of claims 1, 8, 12, 20 and 84-94 as failing to comply with the enablement requirement, Applicants assert that a primary concern raised by the Examiner is the fact that the claim relies on a single patient sample and Applicants have not demonstrated that the invention works with samples beyond seminal fluids, and that different MS probe surfaces might provide different results. Applicants further assert that a secondary concern raised by the Examiner rely on background publications reminding readers that protein fingerprinting-based MS assays suffer from a host of potential problems including machine sensitivity, reproducibility, sample handling, and the manner and timing of sample acquisition from the patient. In response to these concerns, Applicants contend that they have amended the claims and provided a Rule 132 declaration by co-inventor Dr. Tai-Tung Yip. In response to the Examiners concerns raised that the observation of a low molecular weight shift in protein markers between patients with prostate cancer and benign prostate hyperplasia might be restricted to the specific chemistry used to absorb the proteins to the MS probe, Applicants assert that Dr. Yip provides evidence in his declaration that the claimed observation was demonstrated using two additional surface chemistries (see Exhibit 1 of the Declaration). In response to the Examiners concerns raised that the initial work was done with a sample from a single patient and raised a concern that the invention might not be reproducible across a larger patient population, Applicants assert that Dr. Yip provides the Examiner with a copy of two published papers, Adam et al. (2002) Cancer Research 62: 3609-3614 and Cazares et al. (2002) Clinical Cancer Research 8: 2541-2552. Specifically, Applicants assert that in the Adam paper, serum samples were used, whereas in the Cázares paper, prostate tissue samples

were used. Thus, Applicants submit that Dr. Yip explains that these 2002 papers provide amle evidence that prostate cancer patients have a significant increase in lower molecular weight proteins in their serum and prostate-related tissues and fluids compared to patients with benign prostate hyperplasia. In response to the Examiners concerns relating specifically to the prostate cancer assay, wherein only seminal fluid was used and the claims read on other fluids and tissue samples, Applicants assert that the claim have been amended to recite the body samples from which they can provide actual evidence of the invention working. In response to the Examiners secondary concerns raised and references cited with respect to instrument variations, sample handling, the containers used to hold the samples, controlling for patient variables such as diet, stage of disease and patient condition, loss of markers due to binding of small proteins to larger more abundant proteins and the like, Applicants assert that Dr. Yip explains that these secondary issues are applicable not only to the claimed assay, but to any MS-based assay looking at protein fingerprinting for diagnostic purposes. Moreover, Applicants contend that Dr. Yip goes on to explain that most, it not all, of these variables are routinely avoided by those of skill in the art. Furthermore, Applicants contend that so long as the concerns are avoided by good laboratory practices that are routinely practiced by those of skill, patent applications should not have to address such issues to establish hat their assay are enabled. As final evidence that MS protein-based fingerprinting has become widely accepted as an appropriate basis for diagnostic assays, Applicants submit a recent press release from Ciphergen (Exhibit A) which details their recent success in a multi-center validation study with a diagnostic assay for detecting ovarian cancer using protein fingerprinting.

These arguments have been carefully considered and have been found to be persuasive with respect to what the specification is enabled for, as set forth above. However, it the Examiners opinion that these arguments, as well as Dr. Yip's declaration, have not been found persuasive with respect to the full scope of the instant claims.

In order to expedite prosecution with respect to Applicants arguments and Dr. Yip's declaration, the Examiner agrees with the following: 1) the abundance of lower weight proteins in prostate cancer samples can be detected with other MS probe surfaces; 2) the abundance of lower weight proteins in prostate cancer samples can be detected in other patients; 3) the abundance of lower weight proteins in prostate cancer patients can be detected in samples other than serum; and 4) that the secondary issues can be routinely addressed by competent laboratory technicians.

However, the Examiner recognizes, as noted in the Yip Declaration as a quotation from Adam (page 3 of Yip), "The successful use of the prostate classification system described herein relies on the protein fingerprinting of the nine masses. Because these masses were found to be reproducibly reliably detected, only the mass values are required to make correct classification or diagnosis." In other words, it appears that one of skill must first identify a reproducible mass value and than use this mass value for correct classification and diagnosis. In the instant case, the claims encompass determining by mass spectroscopy a test amount of a plurality of protein markers in a sample, the protein markers having an apparent molecular weight of less than 10,000 Da and comparing a test amount of the plurality of protein markers having an apparent molecular weight of less than 10,000 Da with an amount of a plurality of protein markers having an apparent molecular weight of less than 10,000 Da from a control sample where the control sample originates from benign prostate hyperplasia and determining if the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia. However, the claims do not recite how to determine whether the test amount in any and/or all samples is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia. While, the specification has taught a number of mass values obtained from a prostate cancer patient's seminal plasma, these mass values do not appear to be identical or reproducible from the mass values obtained from Adam's serum samples or Cazares et al.'s prostate tissues samples. As such, one of skill would need to first identify mass values from prostate tissue, blood, serum, semen, seminal fluid or seminal plasma, which are reproducibly reliably, detected from each of these samples and than use these mass values for classification and diagnosis. Thus, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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